UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/307,223	05/07/99	VARNER J	6627-PA11

HM12/0309

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EXAMINER	
UNGAR, S	
ART UNIT	**PAPER NUMBER**
1642	9

DATE MAILED: 03/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/307,223	Applicant(s) Varner et al
	Examiner Ungar	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Jan 16, 2001*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-79* is/are pending in the application.

Of the above, claim(s) *6-8, 15-18, 21-54, 73, 74, and 76-79* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-5, 9-14, 19, 20, 55-72, and 75* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Election filed January 16, 2001 (Paper No. 8) in response to the Office Action of August 10, 2000 (Paper No. 5) and the Letter of December 12, 2000 (Paper No. 8) is acknowledged and has been entered. Claims 1-79 are pending in the application and Claims 6-8, 15-18, 21-54, 73-74 and 76-79 have been withdrawn from further consideration by the examiner under 37 CAR 1.142(b) as being drawn to non-elected inventions. Claims 1-5, 9-14, 19-20, 55-72 and 75 are currently under prosecution.

2. Applicant's election with traverse of Group I, claims 1-20 and 55-75 in Paper No 8 is acknowledged. The traversal is on the ground(s) that the inventions have not been shown to be distinct and that examination of all groups would not impose a serious burden on the examiner because the claimed inventions are closely related. Applicant further argues that separate classification alone is not acceptable grounds for restriction and that the classes cited have overlapping subject matter. This is not found persuasive. The inventions of the various groups are distinct for the reasons set forth in Paper No. 5. As to the question of burden of search, the inventions are classified differently, necessitating different searches in the US Patent shoes. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group.

Applicant's election with traverse of the species of neoplastic tissue, carcinoma, in Paper No. 8 is acknowledged. The traversal is on the grounds that the inclusive claims are drawn to a method of reducing angiogenesis and the process

of endothelial cell migration is functionally identical in all tissues. The argument drawn to ocular pathology has been found persuasive and the species of neoplasm and ocular pathology are rejoined. Further, upon review and reconsideration the species of sarcoma has been rejoined to the carcinoma species. However, the argument drawn to the other species has been considered but has not been found persuasive because different searches and issues are involved in the examination of each species and the search of each species represents an undue burden. Applicant further argues that biological mechanisms involved in neovascularization occur in a variety of tissues and pathological conditions and cites US Patents. The argument has been considered but has not been found persuasive because each case must be examined on its own merits and for the reasons previously set forth and above, the species requirement is maintained.

Upon review and reconsideration and in view of Applicant's arguments, the requirement for species election drawn to administration of the agent is withdrawn.

Applicant's election with traverse of the species of peptide in Paper No. 8 is acknowledged. The traversal is on the grounds that while the agents vary in structure they remain identical in objectives, method steps dosages and/or schedules used, response variables and criteria for success and are therefore not distinct. The argument has been considered but has not been found persuasive. Applicant admits on the record that the species are different in structure. They are clearly different in mechanism of action, method steps, dosages and response variables. For the reasons previously set forth, the species requirement is maintained.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Specification

4. The specification on page 1 should be amended to reflect the status of the parent application. It is noted that benefit is claimed to a 06 series provisional application. Appropriate correction is required.

Abstract

5. The Abstract of the Disclosure is objected to because:

(A) the abstract is titled "Abstract of the Invention". The abstract is not the abstract of the "invention", it is the abstract of the "disclosure". The objection can be obviated by amending the abstract to delete the term "invention" and substituting the term "disclosure";

(B) the abstract is limited to a single paragraph within the range of 50 to 250 words and should not exceed 25 lines of text since the space provided for the abstract on the computer tape by the printer is limited.

See M.P.E.P. § 608.01(b). Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. Claim 2 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite in the recitation of the term "substantially". The term "substantially" is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a

standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

8. Claims 1-5, 9-13, 55-66, 68-69, 71-72 and 75 are rejected under 35 U.S.C. § 102(e) as being anticipated by US Patent No. 5,922,676 as evidenced by WO WO95/14714.

It is noted that platelets secrete fibrinogen (see Gallin et al, Inflammation:Basic Principles and Clinical Correlates, 1988, Raven Press, New York, page 552), thus it is assumed for examination purposes that fibrinogen is expressed in all tissues since platelets are found in all tissues.

The claims are drawn to a method of reducing or inhibiting angiogenesis in a tissue, in an individual, reducing the severity of a pathological condition associated with angiogenesis in an individual, comprising contacting alpha 5 beta 1 integrin in the tissue with an agent that interferes with specific binding of the alpha 5 beta 1 integrin to a ligand expressed in the tissue, thereby reducing or inhibiting

angiogenesis in the tissue (claims 1, 55 and 57) wherein the agent does not substantially interfere with the specific binding of a ligand to an integrin other than alpha 5 beta 1 integrin to its ligand (claim 2) wherein the ligand is fibronectin (claim 3), wherein the tissue comprises ocular tissue (claims 4 and 68), wherein the ocular tissue is selected from the group including retina, macula and cornea (claim 5), wherein the tissue comprises a neoplasm (claims 9 and 58), wherein the neoplasm is malignant (claims 10 and 59), wherein the neoplasm is a metastatic malignant neoplasm (claims 11 and 60) wherein the neoplasm is a carcinoma, a sarcoma (claims 12 and 61-63), wherein the agent comprises a peptide (claim 13), wherein the peptide comprises SEQ ID NO:1 (claim 14), wherein the agent is linked to a cytotoxin (claim 19), wherein the cytotoxin is a cancer chemotherapeutic drug (claim 20), wherein the individual is a human (claims 56 and 64), wherein the carcinoma is selected from the group including breast carcinoma, colon carcinoma, ovarian carcinoma and pancreatic carcinoma (claim 62) wherein the malignant neoplasm is a sarcoma (claim 63), wherein the agent is administered iv (claims 65 and 71), administered orally (claim 66 and 72), wherein the pathological conditions are selected from the group including diabetic retinopathy and macular degeneration by neovascularization (claim 69), wherein the agent is administered at a dose of 0.0001 to 100 mg/kg body weight (claim 75).

It is noted that the term "peptide" as defined by the specification is broadly used to include oligomers and polymers of amino acids that are linked by a peptide bond. The specification further states that the term peptides includes molecules

commonly referred to as peptides which generally contain two to about fifty amino acids. It is assumed, for purposes of examination, this definition is not limiting.

WO95/14714 specifically teaches that the only known ligand for alpha 5 beta 1 integrin is fibronectin (page 2, lines 3-4).

US Patent No. 5,922,676 teaches a method of inhibiting angiogenesis and treating pathologies with angioproliferative components comprising administering superfibronectin (sFN) to a subject. Superfibronectin is a multimer of fibronectin (col 4, lines 11-15). The pathologies to be treated with the method include cancer, ocular neovascularization, diabetic retinopathy and in particular the patent provides methods for inhibiting metastasis of osteosarcoma and colon, breast or ovarian carcinoma (col 2, lines 35-48). The effective amount to be administered can be about 0.1 micrograms/kg to about 100 mg/kg body weight (col 8 (lines 55-60). US Patent No. 5,922,676 specifically teaches that sFN is a form of fibronectin (col 1, lines 55-60) and teaches that the term "subject" as used in the patent means a vertebrate, preferably a mammal and in particular, a human (col 5, lines 63-64). Further, the term "administering" comprises any method of administration known to one skilled in the art including intravenously orally and topically (col 9, lines 20-40). Although the reference does not specifically state that the method comprises contacting alpha 5 beta 1 integrin with an agent that interferes with specific binding of the alpha 5 beta 1 integrin to its ligand or that the ligand is fibronectin or that the agent does not substantially interfere with the binding of a ligand to an integrin other than alpha 5 beta1, the claimed method appears to be the same as that of the prior art method absent a showing of unobvious differences. The office does not have the

facilities for examining and comparing applicant's method with the method of the prior art in order to establish that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed method is functionally different than that taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

10. Claim 1-5, 9-14, 19-20, 55-72 and 75 are rejected under 35 U.S.C. § 103 as being unpatentable over US Patent No. 5,922,676 in view of WO95/14714 and

Thorpe (Monoclonal Antibodies in Biological and Clinical Applications, Pinchera et al eds, 475-506, 1985).

The claims are drawn to a method of reducing or inhibiting angiogenesis in a tissue, in an individual, reducing the severity of a pathological condition associated with angiogenesis in an individual, comprising contacting alpha 5 beta 1 integrin in the tissue with an agent that interferes with specific binding of the alpha 5 beta 1 integrin to a ligand expressed in the tissue, thereby reducing or inhibiting angiogenesis in the tissue (claims 1, 55 and 57) wherein the agent does not substantially interfere with the specific binding of a ligand to an integrin other than alpha 5 beta 1 integrin to its ligand (claim 2) wherein the ligand is fibronectin (claim 3), wherein the tissue comprises ocular tissue (claims 4 and 68), wherein the ocular tissue is selected from the group including retina, macula and cornea (claim 5), wherein the tissue comprises a neoplasm (claims 9 and 58), wherein the neoplasm is malignant (claims 10 and 59), wherein the neoplasm is a metastatic malignant neoplasm (claims 11 and 60) wherein the neoplasms is a carcinoma, a sarcoma (claims 12 and 61-63), wherein the agent comprises a peptide (claim 13), wherein the peptide omprises SEQ ID NO:1 (claim 14), wherein the agent is linked to a cytotoxin, chemotherapeutic drug (19-20), wherein the individual is a human (claims 56 and 64), wherein the carcinoma is selected from the group including breast carcinoma, colon carcinoma, ovarian carcinoma and pancreatic carcinoma (claim 62) wherein the malignant neoplasm is a sarcoma (claim 63), wherein the agent is administered iv (claims 65 and 71), administered orally (claim 66 and 72), wherein the ajent is administered into a neoplasm (claim 67), wherein the pathological

conditions are selected from the group including diabetic retinopathy and macular degeneration by neovascularization (claim 69), wherein the agent is administered in the form of eye drops (claim 70) wherein the agent is administered at a dose of 0.0001 to 100 mg/kg of body weight (claim 75)..

US Patent No. 5,922,676 teaches as set forth above and further teaches that teaches that CRRETAWAC, SEQ ID NO:18, is an alpha 5 beta 1 directed peptide. It is noted that the prior art SEQ ID NO:18 is identical to claimed SEQ ID NO:1. US Patent No. 5,922,676 exemplifies the comparison of sFN and SEQ ID NO:18 for tumor metastasis-inhibitory properties drawn to melanoma. Although the reference specifically states that sFN was significantly more effective than SEQ ID NO:18 in inhibiting metastasis, it is clear from a review of Figure 8B that, other than two outlyers, the effects of SEQ ID NO:18 on tumor metastasis are substantially the ssame as sFN in inhibiting melanoma metastasis (see col 27 and Figure 8b). It does not appear that statistical analysis would reveal any significant differences.

US Patent No. 5,922,676 teaches as set forth above but does not teach the peptide is SEQ ID NO:1 (claim 14), the peptide linked to a cytotoxin (claim 19), wherein the cytotoxin is a cancer chemotherapeutic drug (claim 20), wherein the agent is administered into a neoplasm (claim 57), wherein the agent is administered by eye drops (claim 70).

WO95/14714 teaches as set forth above and further specifically teaches a therapeutic method useful for inhibiting metastasis of tumor cells expressing alpha 5 beta 1 integrin comprising administering a peptide wherein the peptide selectively binds alpha 5 beta 1 integrin ((p. 4, lines 28-32) whose ligand is fibronectin (page

2, lines 3-4), wherein SEQ ID NO:6 (which comprises claimed SEQ ID NO:1) specifically inhibit cell attachment to fibronectin (figures 5 and 6) and specifically teaches the inhibition of tumor metastasis with peptides of the invention directed toward tumors expressing the alpha 5 beta 1 integrin (para bridging pages 20 and 21), which include SEQ ID NO:6 and SEQ ID NO:12 (which is identical to the claimed SEQ ID NO:1). The reference further teaches that the amounts of peptide to be administered can be determined by the assay shown in figure 1, wherein it is demonstrated that dosages of from 1-1000 micrograms are appropriate for SEQ ID NO:6 (page 21, lines 14-22 and Figure 1).

Thorpe teaches procedures for conjugating agents that target tumor cells to a variety of different moieties, including cytotoxins (see entire article). and teaches that by carrying the cytotoxic agent specifically to the tumor, the rest of the body should encounter relatively low levels of drug and so be spared from harm (p. 475, Introduction).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute SEQ ID NO:6 or SEQ ID NO:12 of WO95/14714 for the sFN of US Patent No. 5,922,676 in the methods of US Patent No. 5,922,676 because both agents bind to alpha 5 beta 1 integrin and because US Patent No. 5,922,676 specifically teaches that SEQ ID NO 18 inhibits cancer cell metastasis in a manner substantially equivalent to that of sFN and WO95/14714 specifically teaches a method useful for inhibiting metastasis using the recited peptides. One of ordinary skill in the art would have been motivated to substitute SEQ ID NO:6 or SEQ ID NO:12 of WO95/14714 for the sFN of US Patent No.

5,922,676 in the methods of US Patent No. 5,922,676 because WO95/14714 specifically teaches the inhibition of tumor metastasis with peptides of the invention directed toward tumors expressing the alpha 5 beta 1 integrin.

It would have been *prima facie* obvious and one of ordinary skill in the art would have been motivated to administer the agent for treatment of ocular pathology by administration of eye drops because US Patent No. 5,922,676 specifically teaches the topical administration of the agent of the invention.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to link the agents of either US Patent No. 5,922,676 or WO95/14714 to a cytotoxin using the method taught by Thorpe. One of ordinary skill in the art would have been motivated to produce the claimed cytotoxin-linked agents in view of the teachings that such cytotoxin-linked agents are useful for diagnosis of refractory tumors and the general knowledge that antibodies can be successfully targeted to tumor cells. Finally, it would have been *prima facie* obvious and one of ordinary skill in the art would have been motivated to inject the agents directly into the tumor in the methods of either US Patent No. 5,922,676 or WO95/14714 in order reduce diffusion and non-specific sequestration of the agents.

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
February 28, 2001